REMARKS

Claims 1-7 are presently pending. New claim 78 has been added. The outstanding rejections are addressed individually below. Applicants also respectfully reassert all arguments presented in the Office Action response dated February 14, 2007.

1. History/Examiner Interview

As an initial matter, Applicants thank Supervisory Examiner Foley, Primary Examiner Canella, and Examiner Joyce for their time and guidance on this matter. It is very much appreciated.

On August 8, 2007, Applicants held a telephonic interview with the Examiners, discussing the various rejections detailed in the Final Office Action of February 14, 2007. Early in the interview, Examiner Joyce had technical difficulties and could not remain on the call. Supervisory Examiner Foley and Primary Examiner Canella completed the interview. Applicants discussed the § 112, first and second paragraph rejections.

During the interview, Applicants stated that the discovery of increased expression of triosephosphate isomerase in multidrug resistant neoplastic cells, particularly on the cell-surface of the cells, indicated that the triosephosphate isomerase is a marker of multidrug resistance. Applicants also discussed the fact that other markers had been discovered using these cell lines, and the results with those markers were confirmed in human cell and tissue samples. In support of this point, Applicants referenced data generated in ovarian cancer cell lines, and other cell lines showing increased expression of triosephosphate isomerase. Applicants also described the use of cell lines in cancer research, and stated that cell lines had been a model for cancer for many years. Applicants further discussed the relevance of Tockman to the claims, arguing that requiring population studies to establish the validity of a marker fell outside of the requirements of patentability. In addition, Applicants explained that the term "detectably greater than" was clear to one of ordinary skill in the art, and pointed to written description support in the specification for the term.

After considering Applicants arguments, Supervisory Examiner Foley and Primary Examiner Canella indicated that the Applicants' arguments appeared to be persuasive, and stated that Applicants should provide such arguments in a response. In particular, Supervisory Examiner Foley and Primary Examiner Canella approvingly noted that the claims were drafted such that the test cell was neoplastic, and the level of expression for triosephosphate isomerase was determined in cancer test cells and control cells. The Examiners then stated that the "detectably greater than" term appeared to be adequately definite and supported in the specification. They observed that the data from the cell lines appeared to be reasonably correlative with detecting multidrug resistance *in vivo*. There also appeared to be agreement that Tockman did not show the need for population studies to validate the data from the cell lines.

The interview ended with Applicants agreeing to submit the arguments presented in the interview.

2. Claim Amendments

Applicants have added claim 78, which depends from claim 1, to recite that a test neoplastic cell is multidrug resistant if the level of cell-surface-expressed triosephosphate isomerase measured on the test cell is detectably greater than the level of cell-surface-expressed triosephosphate isomerase measured on the control, non-resistant cell. Support for this claim can be found, *inter alia*, at page 19, lines 10-15; page 21, lines 18-20; page 26, lines 21-30; page 27, lines 18-29; page 28, lines 17-25; page 34, lines 9-15; page 46, lines 5-16; and Examples 1, 2, 4, and 5.

3. The Term "Greater Than" Is Not Indefinite.

Claims 1-7 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as their invention (see Final Office Action, pg. 2 and the Office Action dated August 10, 2006, pg. 3). Applicants respectfully traverse this rejection.

As an initial matter, Applicants note that claims 1-7 are directed to methods of detecting multidrug resistance by measuring triosephosphate isomerase expression anywhere in a test cell,

and comparing the level of triosephosphate isomerase expression in the test cell to the level of triosephosphate isomerase expression in a control, nonresistant neoplastic cell. In addition, new claim 78, which depends from claim 1, recites that cell-surface-expressed triosephosphate isomerase is measured and a test neoplastic cell is multidrug resistant if the level of cell-surface-expressed triosephosphate isomerase on the test cell is detectably greater than the level of cell-surface-expressed triosephosphate isomerase on the control, non-resistant cell.

According to MPEP § 2171 and § 2173, the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant so as to inform the public of the boundaries of what constitutes infringement of the patent. Under this rationale, acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification (see MPEP § 2173.05(b)). Accordingly, an Examiner must review the claim in its entirety to determine whether the claim at issue apprises one of ordinary skill in the art of its scope, and therefore serves the notice function required by § 112, second paragraph.

Under this analytical framework, the primary inquiry under §112, second paragraph, is whether the claim meets the threshold requirements of clarity and precision, not whether more suitable language is available (see MPEP § 2173.02). Relative terminology in a claim does not render the claim automatically indefinite under § 112, ¶2 (see MPEP § 2173.05(b)). In addition, imprecision of claim terminology does not render a claim indefinite so long as one of ordinary skill in the art would understand the scope of the claimed invention (see MPEP § 2173.05(b)).

Applicants respectfully aver that the use of the term "greater than" does not render claims 1-7 indefinite. As pointed out in the Final Office Action and discussed during the interview, one of ordinary skill in the art recognizes that *de minimus* differences in the level of expression of triosephosphate will occur between different samples due to the variability between detection methods and samples. However, one of ordinary skill in the art also recognizes that this variability can be controlled for by including a control sample. To eliminate the effects of variability, one of ordinary skill in the art compares the level of expression detected in a potentially multidrug resistant cell to the level of expression detected in a *control* sample. In the context of the claims, one of skill in the art of cancer research and therapy would recognize that

the level of triosephosphate isomerase expression in, or on the cell surface of a test neoplastic cell must be detectably "greater than" the level of triosephosphate isomerase expression identified in, or on the cell-surface of a *control,* nonresistant, neoplastic cell. The *control,* nonresistant, neoplastic cell is a *control* cancer cell that has detectably less expression of triosephosphate isomerase protein than multidrug resistant cancer cells. Therefore, the *control,* nonresistant neoplastic cell represents an internal *control* in each experiment that eliminates the effects of differences in expression related to the detection technique that is used rather than differences related to actual expression in the cell samples.

During the interview, Applicants also respectfully noted that the exact "degree" of increased cell surface triosephosphate isomerase expression in the test cell as compared to the *control* nonresistant, neoplastic cell is not important as any amount of triosephosphate isomerase that can be detected in, or on the cell-surface of the test neoplastic cell greater than the amount of triosephosphate isomerase detected in, or on the cell-surface of the control, nonresistant, neoplastic cell is indicative of multi-drug resistance.

Therefore, in view of Applicants' earlier amendment, new claim 78, and this argument, Applicants respectfully request that the rejection of claim 1 be reconsidered and withdrawn.

Likewise, the rejection of claims 2-7, all of which depend from claim 1 and thus contain all the limitations thereof, should be reconsidered and withdrawn.

4. The Term Detectably Greater Than Is Supported In The Specification

Claims 1-7 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement (see Final Office Action, pp. 6 and 7). More specifically, the term "detectably greater than" was not allegedly described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the invention (see Final Office Action, pg. 7). The Final Office Action further alleges that the cited support did not suggest that the enhanced level of triosephosphate isomerase in multidrug resistant cells is "detectably greater than" the amount found in control cells (Final Office Action, pg. 7). Applicants respectfully traverse this rejection.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. (see MPEP § 2163.I, *citing, Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116). The written description requirement, however, does not require *ipsis verbis* (*i.e.*, "in the same words") recitation of the invention to be sufficient (see MPEP § 2163.II.A.3, *citing, Vas-Cath,* 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson,* 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972)). So long as one of ordinary skill in the art, upon reading the specification, can determine that the inventor was in possession of the claimed invention, then the written description requirement is met, even if every nuance of the claims is not explicitly described in the specification (see *id.*).

In the interview, Applicants respectfully asserted that the specification sufficiently describes the subject matter for the term "detectably greater than." The specification provides a specific description of a method in which a level of expression of triosephosphate isomerase is *detected* in multidrug resistant cells or cells having multidrug resistance potential, and compared to the level of expression detected in a control, nonresistant neoplastic, whereby the level of expression in the multidrug resistant cell is greater than the level of expression of triosephosphate isomerase in control, nonresistant neoplastic cells (see Specification, pg. 3, lines 17-23). The specification also teaches that this level of expression must *detected* and methods of detecting the level of expression of triosephosphate isomerase (see Specification, pg. 26, lines 25-30 and pg. 30, lines 5-22). Therefore, the specification properly describes the subject matter, evidencing that the Applicants were in possession of the claimed invention.

Accordingly, Applicants respectfully request that this § 112, first paragraph rejection of claim 1 be reconsidered and withdrawn.

Likewise, the rejection of claims 2-7, all of which depend from claim 1 and thus contain all the limitations thereof, should be reconsidered and withdrawn.

5. *Cell Lines Are A Reliable and Predictable Model of Primary Tumors And Therefore Merely Routine Experimentation Is Required To Practice The Claimed Invention*

Claims 1-7 also stand rejected under 35 U.S.C. § 112, first paragraph. The Office Action dated August 10, 2006 ("the Office Action") opined that "undue experimentation" is required to practice the claimed invention because the specification does not provide sufficient disclosure to establish that cell surface-expression of triosephosphate isomerase on multidrug-resistant cell lines correlates with multidrug resistance in tumors *in vivo* (see the Office Action, pp. 4-7). The Office Action based its allegations of lack of enablement on prior art references that allegedly establish that there is no correlation between the results identified *in vitro* and the cell characteristics or behavior found *in vivo*. The rejection was maintained in the Final Office Action dated February 14, 2007 ("the Final Office Action") (see the Final Office Action, pp. 4-5). Applicants note that the Final Office Action refers to a rejection under § 112, second paragraph. Applicants assume that the rejection is being made under § 112, first paragraph, and respectfully traverse the rejection as being a rejection under § 112, first paragraph.

According to MPEP § 2164.05(b), the specification must be enabling to those of skill in the relevant art to which the claimed invention pertains at the time the application was filed. A disclosure can be enabling, while requiring experimentation to perform the claimed invention, provided that the experimentation required is not "undue." The quantity of experimentation needed to be performed by one of skill in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention (see MPEP § 2164.06). However, the test is not "merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed" (see MPEP § 2164.06). In the chemical arts, time and difficulty of experiments are not determinative if they are merely routine (see MPEP § 2164.06).

In addition, enablement of a claimed invention requires a correlation between the *in vivo* or *in vitro* model used in the application and the disclosed method of use (MPEP § 2164.02). The issue of correlation is dependent on the state of the art. If the prior art shows that a correlation exists between a particular model and a specific condition, then it should be accepted

as correlating unless the examiner has evidence that the model does not correlate (MPEP § 2164.02). It should be noted that a rigorous or invariably exact correlation is not required where the disclosure of pharmacological activity is reasonable based upon the probative evidence (MPEP § 2164.02, quoting *Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed.Cir. 1985)).

Applicants respectfully assert that a correlation exists between established cancer cell lines and primary tumors. As pointed out in the Examiner interview, the cell lines used in the specification and examples, such as SKOV-3, have been used to study cancer and multidrug resistance for more than a decade (see, *e.g.*, Langton-Webster *et al.* (1994) *Cell Growth Diff.* 5:1367-1372; Husain *et al.* (1998) *Cancer Res.* 58:1120-1123; Aebi *et al.* (1996) *Cancer Res.* 56:3087-3090; Duan *et al.* (1999) *Clin. Can. Res.* 5:3445-3453). Thus, those of skill in the art have recognized the useful correlation between cell lines and in tumors, and use cell lines, particularly the ones used in the application, as models for *in vivo* cancer.

In light of such a correlation and in view of the specification teachings, Applicants aver that merely routine experimentation would be required to practice the claimed invention. For example, the application provides detailed disclosures on how practice the claimed invention. Specifically, the application discloses how to make and use triosephosphate isomerase-binding agents, which are used to bind to, and in some cases detect, triosephosphate isomerase protein in neoplastic cells (see specification, pg. 32, l. 27-pg. 56, l.10). Moreover, the application discloses how to obtain control, nonresistant, neoplastic cells and from where to obtain test neoplastic cells (see specification, pg.28, l. 27-pg. 30, l. 8; Example 4 and 5). The specification also teaches exemplary embodiments of the claimed invention (see specification, pg. 30, l. 21-pg. 32, l. 17; Examples 4 and 5). For example, test neoplastic cells and control, nonresistant, neoplastic cells are isolated and fractionated to yield plasma membrane fractions (see specification, pg. 30, ll. 25-26). Therefore, the specification provides adequate teachings to allow one of skill in the art to practice the claimed invention with merely routine experimentation.

Accordingly, Applicants respectfully request that this § 112, first paragraph, rejection be reconsidered and withdrawn.

Likewise, the rejection of claims 2-7, all of which depend from claim 1 and thus contain all the limitations thereof, should be reconsidered and withdrawn.

6. The Claimed Invention Does Not Require Validation

Claims 1-7 stand rejected under 35 U.S.C. § 112, first paragraph, based on the contention that the triosephosphate marker requires further validation in human populations (see the Final Office Action, pg. 5 and 6). The Office Action dated August 10, 2006 opined that the Tockman reference (Tockman *et al.* (1992) *Cancer Res.* 52:2711s-2718s) ("Tockman") teaches that validation is necessary to establish successful application of a marker and to show that the invention will function as claimed (see the Office Action, pg. 8). The Final Office Action maintains the previous rejection, and further states that "the general teaching of Tockman is that predictive cancer biomarkers, *in order to be useful as such*, must be validated" (see the Final Office Action, pg. 6). Applicants note that the Final Office Action refers to a rejection under § 112, second paragraph. Applicants assume that the rejection is being made under § 112, first paragraph, and respectfully traverse the rejection as being a rejection under § 112, first paragraph.

According to MPEP § 2164, the enablement requirement demands that the specification of an application describe how to make and use a claimed invention. Enablement merely requires that the specification describe the claimed invention to the interested public in a meaningful way (see MPEP § 2164). However, compliance with 35 U.S.C. § 112 does not require that the specification "enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect" (see § 2164).

As discussed in the Examiner interview, the MPEP clearly states that Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials to satisfy utility in pharmacological applications (see MPEP § 2107.03.IV). Also, there is no decisional case law that requires an applicant to provide data from human clinical trials, even with respect to situations where no art-recognized animal models existed for the human disease encompassed by the claim (see MPEP § 2107.03.IV, *citing*, *Ex parte Balzarini*, 21 USPQ2d 1892 (Bd. Pat. App. & Inter. 1991)). It is additionally improper for Office personnel

to request evidence of safety in the treatment of humans, or regarding the degree of effectiveness. (MPEP § 2107.03.IV, *citing*, *In re Sichert*, 566 F.2d 1154 (CCPA 1977)).

During the Examiner interview, Applicants asserted that the Tockman reference does not establish that a marker must be tested against population studies prior to being recognized or established as a diagnostic marker. Those skilled in the cancer research art have identified markers without such testing. Tockman continually teaches that markers should be validated prior to clinical application through population studies (see Tockman, 2711s-2718s). One of ordinary skill in the art would view such teachings as directed to satisfying requirements necessary for using the marker in the clinical setting. The *only* way to sell, and use, a marker in a clinical setting is to provide data through clinical trials to regulatory bodies, such as the FDA, that shows the marker's efficacy and safety. Thus, those of skill in the art would understand the Tockman reference teaches the steps required to obtain regulatory approval for the use of a marker as a cancer detection agent (see Tockman *et al.* (1992) *Cancer Res.* 52:2711s-2718s).

Furthermore, those of skill in the art recognize that the invention works for its intended purpose because the cell lines are well known models for cancer that have been used extensively prior to the filing of the above-referenced application. In addition, cell lines are considered reliable models that produce data that is predictive of cancer and multidrug resistance *in vivo*. Accordingly, the specification enables the claimed invention without the need for further validation because one of skill in the art would expect that the claimed invention works for its intended purpose.

Applicants respectfully assert, as pointed out in the Examiner interview, that they are not under any burden to support the utility of this invention using data from human clinical trials. Those of ordinary skill in the cancer arts do not view human prospective population studies as a prerequisite to show that a potential diagnostic marker has utility or is enabled. Recognizing this, the MPEP states that requiring human clinical trial data is not a prerequisite for establishing utility of a particular pharmacological invention, supporting the understanding of those of ordinary skill in the art that certain markers can be identified as having potential diagnostic value *prior* to being validated through human trials or costly population studies (see MPEP § 2107.03.IV). Accordingly, requiring data from human trials places a burden on Applicants that

goes beyond what is required by the Patent Office or what is recognized by those of ordinary skill in the art to show that a particular marker has value in the diagnostic setting.

Moreover, Applicants assert that the present rejection is logically inconsistent with prior positions taken by the Patent Office with respect to the evidence required to support pharmaceutical/biotechnology inventions. The MPEP recognizes that animal models can be used to identify potential uses of therapeutic drugs so long as there is a reasonable correlation between the art-recognized model and the particular condition (see MPEP § 2164.02). Under this rationale, there are instances in which a method of using a new drug for treating a condition is supported using data from models, such as animal models (see *id.*). By referring to Tockman as requiring prospective population studies to satisfy enablement, the Final Office Action imposes a higher standard of enablement on Applicants for the diagnostic marker of the present invention as compared to the standard explicated in the MPEP for application to biotechnology generally, and to therapeutic agents specifically (see MPEP § 2164.02). Therefore, Applicants respectfully assert that the rejection is logically inconsistent with Patent Office practice for biotechnology inventions.

Accordingly, Applicants respectfully request that the § 112, first paragraph, rejections be reconsidered and withdrawn.

Likewise, the rejection of claims 2-7, all of which depend from claim 1 and thus contain all the limitations thereof, should be reconsidered and withdrawn.

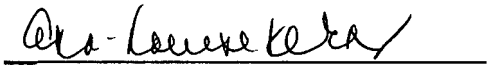
CONCLUSIONS

In view of the arguments set forth above, Applicants respectfully request the rejections contained in the Office Action mailed on February 14, 2007 be reconsidered and withdrawn. Applicants also submit that the pending claims are in condition for allowance.

The time for responding to this action has been extended to August 14, 2007 by the accompanying Petition for a Three Month Extension of Time and payment of fee. No additional fees are due in connection with this response. However, please charge any underpayments or credit any overpayments to Deposit Account No. 08-0219.

If the Examiner believes that any further discussion of this communication would be helpful, please contact the undersigned at the telephone number provided below.

Respectfully submitted,



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